Lactic Acidosis and Phenformin Intoxication

Report of Two Cases with Review of Literature

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SINCE Ungar and coworkers[24] drew attention to the hypoglycemic effect of phenformin (N′-β-phenethylbiguanide) in different species of animals, this drug has been widely used in this country. Even so, the mechanism of action is still not clear.[6,20,25,28] Steiner and Williams[20] suggested that hypoglycemia caused by phenformin is achieved through the so-called "Pasteur effect" with acceleration of anaerobic glycolysis and resultant accumulation of lactic acid. Metabolic acidosis in patients on phenformin has been reported, [10,17,25,26,27] which Walker and coworkers[25] and Lexow[17] suggested might be caused by increased lactic acid production. This view has been supported by in vitro studies of Tyberghein and Williams.[23] There is also in vivo evidence that hyperlacticemia with slow elimination of serum lactic acid after exercise occurred in patients taking phenformin[3,8,25]; but Bernier and coworkers[2] and Shepardson and his associates[19] were not able to confirm this.

Lactic acidosis as a clinical entity with definite diagnostic and prognostic criteria was emphasized by the investigations of Huckabee.[11-15] Phenformin as a cause of so-called "irreversible" lactic acidosis (group 2B patients as defined by Huckabee) was documented in six cases.[2,7,21] Although the evidence for phenformin as the etiologic agent was strong, this was not definitely proved inasmuch as all of the patients were in shock with the exception of one case[7] in which acidosis appeared to precede shock. Other investigators, including Danowski, also questioned that phenformin is the primary etiologic agent in "the lactic acidosis syndrome."[4]

Two patients, both diabetic and both receiving phenformin therapy, were recently clinically evaluated at San Joaquin General Hospital, Stockton.

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Reports of Cases

CASE 1. A 62-year-old white woman with chronic alcoholism and diabetes of eight years' duration, was admitted on August 30, 1963, to San Joaquin General Hospital for the tenth time because of preexisting hemiparesis, incontinence of urine and feces, and a family care problem.

Her previous admissions dated back to 1951 when she was admitted for chronic alcoholism and bronchitis. She was found to have diabetes mellitus in 1955, and hepatic cirrhosis was confirmed by liver biopsy in 1956. Reasons for admission on other occasions included a Colles fracture, pneumonia, dislocated left shoulder with fractured left humeral head, chronic alcoholism, diabetes mellitus and left hemiparesis with mental deterioration. Her diabetes was mild in nature and it was well controlled with 10 units of NPH insulin daily. An electrocardiogram taken in 1961 was within normal limits.

The patient was obese, had blood pressure of 180/80 mm of mercury, a pulse rate of 96 per minute, a respiratory rate of 20 per minute and body temperature of 100°F. She was disoriented and confused. Other significant physical findings included absence of pedal pulses and left femoral pulse, diminished right femoral and carotid pulses, and generalized weakness. Heart, lung and abdominal examinations were within normal limits.

Admission laboratory work showed a hematocrit of 37 volumes per cent, leukocytes numbering 9,000 per cu mm with a normal differential count, blood urea nitrogen of 18.5 mg, creatinine of 0.6 mg and fasting blood sugar of 99 mg per 100 ml. Urinalysis showed a two plus reaction for albumin and moderate bacteriuria, 10 to 20 red blood cells and 5 to 10 white blood cells per high power field, but no sugar and no acetone. Coliform bacilli were cultured from the urine. An x-ray film of the chest was within normal limits.

Initial impression was (1) old cerebrovascular accident with left hemiparesis, (2) diabetes mellitus with questionable renal lesion, (3) Laennec's

cirrhosis, (4) generalized arteriosclerosis with chronic brain syndrome.

The therapeutic plan was to attempt to control the diabetes with oral hypoglycemic agents, then to transfer the patient to a nursing home for further care.

The patient's course in the hospital was unremarkable. She was given an 1,800 calorie diabetic diet. Tolbutamide 0.5 gm twice a day was started on September 2, 1963, and increased to 1 gm three times a day by September 14, 1963. Because of poor control of diabetes, chlorpropamide 250 mg twice a day was tried on September 17, 1963, but this also met with failure. Up to this time the fasting blood sugar ranged between 180 and 220 mg per 100 ml. Administration of phenformin timed disintegration tablets, 50 mg twice a day was initiated on September 24, 1963, and tetracycline 250 mg every six hours was started on September 26, 1963, because of continued bacteriuria. On September 29, 1963, the patient vomited twice, complained of slight abdominal pain, and refused to eat. She was thought to have diabetic acidosis, although her pulse, blood pressure and respiration were stable. Blood sugar was 170 mg per 100 ml with a negative reaction for serum acetone. Serum electrolyte studies showed total carbon dioxide of 8.7 mEq, sodium of 142 mEq, chloride of 106 mEq, and potassium of 5.4 mEq per liter. The patient was given 15 units of regular insulin and the next day she was found to be perspiring profusely, her skin was cold and clammy and she was unable to answer questions. The blood pressure was 120/60 mm of mercury, the pulse was 120 per minute and the fasting blood sugar was 179 mg per 100 ml. The urine was negative for acetone. An electrocardiogram showed no evidence of myocardial infarction and no changes compared with one taken a year previously.

On October 1, 1963, phenformin was discontinued and therapy was changed to 20 units of NPH insulin daily. The blood pressure at that time was 130/70 mm of mercury. Total carbon dioxide was 8.3 mEq per liter of serum and the blood sugar was 72 mg per 100 ml. The hypoglycemic symptoms were relieved by intravenous administration of glucose. Next day the blood urea nitrogen was 108 mg and blood sugar 76 mg per 100 ml and the blood pH was 7.2. Serum lactic acid* was reported to be 107 mg per 100 ml (normal 5 to 20 mg). The blood pressure ranged between 60/0 and 70/50 mm of mercury. Diaphoresis continued but the patient would open her eyes when her name was mentioned. Treatment included 5 per cent dextrose in water intravenously (1,000 ml in 8 hours) with 10 units of aqueous insulin and 1 ml Borocca C® (parenteral vitamin B complex with C) per liter of solution, nasal oxygen, 50 mEq of potassium chloride daily, and a total of 500 ml of sodium bicarbonate solution (0.89 mEq per ml strength) intravenously at 20 drops per minute. No attempt was made to treat the hypotension with vasopressor agents. After 12 hours of therapy total serum carbon dioxide was 40 mEq, sodium 135 mEq, chloride 85 mEq, and potassium 3.5 mEq per liter, and blood sugar was 360 mg per 100 ml. Urine was negative for acetone, and blood urea nitrogen was 36 mg per 100 ml. On October 4, 1963, carbon dioxide was 34, sodium 138, chloride 102 and potassium 4.1 mEq per liter. Blood urea nitrogen was 27 mg and fasting blood sugar was 200 mg per 100 ml. Leukocytes numbered 7,000 cu mm with differential count within normal range. The patient was ambulating with help. The electrolytes remained stable thereafter, and the patient's blood sugar was controlled by administration of 15 units of NPH insulin daily. On October 29, serum lactic acid was 11 mg per 100 ml and pyruvic acid was 0.2 mg per 100 ml (normal 0.5 to 1.5 mg). The patient was transferred to a nursing home.

CASE 2. A 69-year-old white woman was admitted November 7, 1963, to San Joaquin General Hospital for the first time with chief complaints of nausea, vomiting and lethargy of five hours' duration. According to the referring physician and to her family, she was known to have had diabetes for five years and hypertension for seven years. For the past year, diabetes was controlled with diet and phenformin, 25 mg three times a day. The patient was also taking Enduronyl® (methychlorthiazide and deserpidine) twice a day for hypertension. Since February 1963, she had noted intermittent episodes of nausea, vomiting and diarrhea. She was found to have pyuria, bacteriuria and azotemia (non-protein nitrogen —125 mg per 100 ml) in March 1963, and an upper gastrointestinal series at that time showed a cicatrized duodenal ulcer and pronounced calcification of the abdominal vessels. Sulfamethoxazole (Gantanol®) was given for the urinary tract infection.

*Determined by Bioscience Laboratory in Los Angeles using the method of Barker and Summerson.[1]

On physical examination the patient was obese and appeared seriously ill. The temperature was 98°F, the pulse rate was 74 per minute, respirations 22 per minute and the blood pressure 140/80 mm of mercury. (In March 1963 it had been 150/80.) The veins in the neck were flat, the lungs were clear with no evidence of pleural effusion. The liver was not enlarged or tender to palpation and there was no pitting edema of the extremities. The heart was enlarged but no murmurs were heard. The peripheral pulses were palpable bilaterally, and results of a neurological examination were within normal limits.

Urinalysis was within normal limits, with specific gravity of 1.010 and no reaction for sugar or acetone. The hematocrit was 36 volumes per cent. Leukocytes numbered 20,300 per cu mm with the cell differential within normal range. Blood urea nitrogen was 44 mg and blood sugar 206 mg per 100 ml. Reaction for serum acetone was negative. Carbon dioxide was 4.4 mEq, chloride 91 mEq, sodium 138 mEq and potassium 3.9 mEq per liter. An x-ray film of the chest showed no abnormalities. An electrocardiogram was consistent with left ventricular hypertrophy but there was no evidence of acute myocardial infarction.

The admission impression was lactic acidosis secondary to phenformin intoxication, arteriosclerotic heart disease with hypertension and left ventricular hypertrophy, and chronic duodenal ulcer by history. Blood specimens were obtained for determination of serum lactic acid and pyruvic acid (1:6 plasma-trichloroacetic acid filtrate), and the contents were reported to be 210 mg and 0.9 mg per 100 ml, respectively.

The patient was treated with 1,500 ml of 5 per cent dextrose in water and sodium bicarbonate (66.7 mEq) infused over a four-hour period. Electrolyte studies three hours after treatment showed carbon dioxide of 7 mEq, chloride of 69 mEq, sodium of 130 mEq and potassium of 5.3 mEq per liter, sugar of 288 mg per 100 ml. Reaction for serum acetone was negative. The patient went into shock with cardiac arrest despite vigorous treatment and died seven hours after admission.

At autopsy bilateral pulmonary edema was observed. The heart showed left ventricular hypertrophy and pronounced myocardial fibrosis. The liver and kidneys were grossly normal.

Microscopic examination showed myocardial fibrosis, atrophy of pancreatic acini, ectasia of pancreatic ducts, normal pancreatic islet cells, cystic atrophy of the endometrium and a nodular colloid goiter. The kidneys showed arterial nephrosclerosis, focal chronic pyelonephritis and decided cloudy swelling of the epithelium of the distal convoluted tubules.

Comment

Huckabee[14,15,16] observed that hyperlactatemia can be induced by hyperventilation or by infusion of glucose, insulin or epinephrine. The increase in serum lactate in these conditions is associated with a concomitant rise in serum pyruvate, so that the serum lactate to pyruvate ratio of 10:1 is maintained (Group 1). Hyperlactatemia is also observed in conditions associated with severe hypoxemia and circulatory collapse, in which greater than 60 per cent "excess" lactate (XL)* is obtained with an increase in serum pyruvate. These can be reversed by treatment of the basic disorder with oxygen administration or by transfusion (Group 2A) and by administration of methylene blue.[22] There is yet another condition associated with the presence of "excess" lactate in which neither hypoxemia nor circulatory collapse is present, and in which the immediate cause is not apparent (Group 2B). Huckabee proposed that it is due to tissue anorexia and he called it "lactic acidosis." Patients in this group often die, and treatment with alkali is often futile.

The diagnosis of lactic acidosis is made by exclusion of other causes of acidosis and by showing the presence of excess lactate in the serum. A thorough history and physical examination, serum electrolyte studies, determination of arterial blood pH and oxygen saturation, renal function tests and determination of blood acetone are essential aids. When acidosis cannot be accounted for, lactic acidosis should be suspected and serum lactic acid and pyruvic acid levels should be checked.

While lactic acid and blood pH determinations were available in Case 1 and both lactate and pyruvate were measured in Case 2, arterial oxygen saturation could not be measured due to limited laboratory facilities. Since pyruvic acid was not

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$$*XL = (L_1 - L_0) - (P_1 - P_0)\frac{L_0}{P_0}$$

L_1 = observed lactate
P_1 = observed pyruvate
L_0 and P_0 = normal values for lactate and pyruvate
Excess lactate is derived from the equation
Lactic acid + DPN $\rightleftarrows$ DPNH + pyruvic acid

done initially in Case 1, we cannot determine whether hyperlactatemia was due to the presence of "excess" lactate or not. However, the patient was resting in bed, was not hyperventilating and was not receiving any medicine except for phenformin and tetracycline. She probably did not belong to Group 1 patients described by Huckabee. Clinically, she was not anoxic and her condition did not improve with nasal administration of oxygen. Acidosis preceded shock in this case, and the acidosis alone was treated without specific shock therapy. The fact that shock reversed after correction of the acidosis would suggest that lactic acidosis may be the cause of the circulatory collapse. For this reason, it would be unlikely that this case of lactic acidosis belonged to Group 2A. However, the improvement of the patient is unusual, since only one patient with lactic acidosis reported to date has survived, and in that case hemodialysis was carried out.[7] There have been no reports of survival in this group with alkali therapy alone. Tranquada[21] showed that the blood phenformin level rose (up to 20 mg per ml) when the drug was given to patients with poor renal function. In the cases he reported, the patients died of lactic acidosis. Daweke[6] suggested that a normal therapeutic level of biguanide (4 to 5 mg per ml) would not cause an increase in blood lactic acid, whereas a "high" level would. However, he did not specify what this level was. In Case 1 herein reported, there was laboratory evidence of poor renal function and the patient could possibly have had elevated blood phenformin, resulting in lactic acidosis, even when she was taking therapeutic doses of phenformin.

Based on our experience in Case 1, the diagnosis of lactic acidosis (Group 2B) was more obvious in Case 2 in light of the calculated "excess" lactate. The patient was azotomeic, but this condition was probably not severe enough to cause acidosis of the degree noted. She was not in diabetic acidosis, as judged by a negative reaction for serum acetone and only slight elevation of blood sugar. Acute myocardial infarction can sometimes cause circulatory collapse and lactic acidosis, but the patient did not have electrocardiographic evidence of acute myocardial infarction, and only myocardial fibrosis was found at autopsy.

From our experience with the two cases herein and the reported experience of other investigators,[2,21] we believe that acidosis preceded shock, and that lactic acidosis in these cases were not caused by shock. We were well aware that pulmonary edema can cause anoxia, which may induce lactic acidosis.[14] The clinical course of the patient in Case 2 was followed very closely, and we were satisfied that at no time was there any physical evidence of pulmonary edema. An x-ray film of the chest supported that belief. It is believed that the pulmonary edema noted at autopsy was acute in nature and probably occurred terminally. All the known causes for lactic acidosis as discussed by Huckabee[14-16] seem to be unlikely in this case, and there is reason to suspect phenformin intoxication as the cause of death.

The issue of the causal relationship between phenformin toxicity and "irreversible" lactic acidosis is further confused by a recent report of Daughaday and coworkers.[5] These investigators reported at least two documented cases in which lactic acidosis developed in patients who were not taking phenformin. This would suggest that diabetes alone can lead to lactic acidosis. It is possible, therefore, that in reported cases in which lactic acidosis developed in diabetic patients taking phenformin, the disease and not the drug was the cause. Daughaday[5] and Huckabee[16] both suggested that tissue anoxia may be the cause of lactic acidosis. It is conceivable, therefore, that a drug like phenformin could trigger the formation of lactic acidosis in a diabetic patient who is susceptible to the development of lactic acidosis. One wonders if phenformin could induce lactic acidosis in a non-diabetic person, with or without poor renal function. In order to establish a causal relationship between phenformin and lactic acidosis, many variables such as are encountered in daily clinical practice should be eliminated. Perhaps this may be accomplished in controlled animal experiments.

Danowski[4] and Huckabee[16] pointed out that death can occur even though serum carbon dioxide and blood pH are corrected, for the serum lactate level might still be elevated. This would imply that lactic acidosis causing death might be more than simple acid-base imbalance; that it may be a reflection of severe tissue anoxia of an irreversible nature.

Phenformin does not lower blood sugar in normal humans, but it does in animals.[28] It exerts its hypoglycemic effect only on persons with diabetes. It is said to inhibit oxidative phosphorylation, thus decreasing Kreb's cycle activity, and to inhibit certain oxidative enzymes, namely, succinic de-

hydrogenase and cytochrome oxidase. The result is tissue anoxia which may lead to increase in glucose uptake by peripheral tissue (Pasteur effect) and increased anaerobic glycolysis, thus explaining the increase in lactic acid production.[28]

The treatment of lactic acidosis has been quite discouraging. Sodium bicarbonate has been tried unsuccessfully. Moore and Bernhard[18] reported successful treatment of hyperlactatemia produced by cardiopulmonary by-pass with a new, nonionic, buffering agent which can traverse cell membranes readily. This is a promising report and worthy of further investigation. Hemodialysis was used successfully by Ewy in one case.[7] More recently, Tranquada[22] reported reversal of the serum lactate and pyruvate ratio in patients treated with methylene blue intravenously, but the patient died.

Before all the conflicting data on the relationship of phenformin to lactic acidosis is resolved and adequate therapy becomes available, a better clarification of the mode of action of phenformin as well as the further reporting of clinical experience with this condition will be necessary.

Summary

Two cases of lactic acidosis associated with phenformin administration in diabetic patients are reported. Both patients were treated with intravenous infusions of alkali. One recovered.

The diagnosis of lactic acidosis was suspected when all common causes for metabolic acidosis were absent. This was confirmed with the demonstration of the presence of serum excess lactate (XL) and a relatively normal or slightly increased serum pyruvate.

The causal relationship between phenformin administration and lactic acidosis was questioned, since lactic acidosis had been reported to occur in diabetic persons who were not taking this drug.

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